32. The method of claim 1, wherein the nerve-related vision disorder is cataract related degeneration.

B2 cont'd

33. The method of claim 1, wherein the nerve-related vision disorder is a detached retina.

34. The method of claim 1, wherein the nerve-related vision disorder is inflammation related degeneration.

35. The method of claim 1, wherein the nerve-related vision disorder is photoreceptor degeneration.

36. The method of claim 1, wherein the nerve-related vision disorder is optic neuritis.

37. The method of claim 1, wherein the nerve-related vision disorder is dry eye degeneration.--

REMARKS

Claims 5 and 7 have been canceled, claims 1, 8, and 9 have been amended, and new dependent claims 22-37 have been added to describe the inventive subject matter more clearly and to place the application in better form for appeal. Upon entry of the above amendments, claims 1-4, 6, 8-11, and 21-37 are pending in the application.

The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Basis for the claim amendments is found on page 16, line 5 to page 17, line 17; page 25, line 1 to page 31, line 2;

page 34, line 20 to page 42, line 20; page 53, line 1 to page 86, line 12; in claims 1, 5, and 7 as originally filed; and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of Claims 1-11 under 35 U.S.C. §112, first paragraph

A. Scope of Enablement for vision disorders

The Office Action rejects claims 1-11 under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the claimed range of visual disorders in sufficiently diverse *in vivo* systems. The Examiner concludes that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims without undue experimentation.

Preliminarily, Applicants note that the Office Action does not address claim 21, which was added in the Response and Amendment filed March 3, 2000.

Without waiving this deficiency, Applicants respectfully traverse this rejection for the reasons stated in the Response and Amendment filed March 3, 2000, which is incorporated by reference herein. The Office Action has failed to establish a *prima facie* case of nonenablement. In that regard, Applicants note that the

Examiner has failed to provide an affidavit under 37 CFR § 1.104(d)(2) or other authority supporting his conclusions in making this rejection.

In order to advance prosecution, Applicants have amended the claims (1) to claim specific, "nerve-related" vision disorders and (2) to claim treating "a mammal", rather than "an animal". Applicants submit that these amendments address both the 'scope of disorders' and 'diversity of *in vivo* systems' bases raised by the Examiner in support of the enablement rejection.

As presently amended, the claims cover the *nerve-related component* of the various enumerated vision disorders. Thus, for example, myopia may secondarily cause or result from one or more nerve-related vision disorder(s). It is well known to one of ordinary skill in the art that the vision disorders disclosed and claimed in the present application may exhibit one or more primary or secondary nerve-related indication(s) or symptom(s)[1]. When used in the treatment of the nerve-related component of a vision disorder, the compounds of the invention are thereby used in a method of treating a component of the disorder, as distinguished from "curing" or "preventing" the vision disorder in its full range of manifestations.

Thus, to consider an example raised by the Examiner, a compound of the invention might be used in a method of treating

myopia in order to reduce or prevent related nerve damage. Reducing or preventing nerve-related damage is itself sufficient to support claims to a method of treating myopia regardless of whether correction of refractive errors is achieved. The amendments address the Examiner's concern about the scope of disorders to be treated and obviate the rejection under 35 U.S.C. §112, first paragraph.

Similarly, the amendments reduce the scope of claimed subjects of the methods of treatment from "animals" to "mammals", and thereby address the Examiner's concern with treating fish, birds, reptiles, and other non-mammals. These amendments obviate the rejection under 35 U.S.C. §112, first paragraph.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

B. Enablement for Treatment of a Memory Disorder

The Office Action rejects claims 1-11 under 35 U.S.C. §112, first paragraph, as lacking enablement for treatment of a memory disorder in diverse animal species, and for treating Alzheimer's Disease, amnesia, and Korsakoff's syndrome specifically.

Applicants again respectfully traverse this rejection for the reasons stated in the Response and Amendment filed March 3, 2000. The Examiner has failed to establish a *prima facie* case of nonenablement. A patent application is presumptively enabled when

filed and the Examiner has failed to provide evidence that "there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971); *35 U.S.C. §112 First Paragraph Enablement Training Manual*, citing *In re Wright*, 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993).

In order to advance prosecution, Applicants have amended the claims to claim treating "a mammal", rather than "an animal". Applicants submit that these amendments address the 'diversity of *in vivo* systems' basis raised by the Examiner in support of the enablement rejection.

The Office Action further asserts that there is a need for additional animal models and *in vivo* experimentation to determine the potential efficacy of the compounds and to establish correlation to *in vivo* treatment.

In the disclosure, Applicants teach a correlation between neurotrophic substances and neurodegenerative disorders, including Alzheimer's Disease, Parkinson's Disease, and ALS. Applicants also teach a correlation between the MPTP model and Parkinson's Disease. Finally, Applicants teach a correlation between the experimental data from the Morris Water Maze and memory improvement. In the absence of adequate reasons advanced by the examiner to establish

that a person skilled in the art could not use the genus as a whole without undue experimentation, representative examples together with a statement applicable to the genus as a whole are sufficient to support the claimed genus.

Further, there is nothing in the Patent Statute which gives the USPTO the right or duty to require an applicant to prove that compounds are effective. (see *In re Krimmel*, 130 USPQ 215 (C.C.P.A. 1961) and *In re Hartop*, 135 USPQ 419 (C.C.P.A. 1962)). This rejection attempts to improperly hold Applicant to a standard appropriate to FDA practice, but inappropriate to practice before the USPTO.

Applicants respectfully submit that additional *in vivo* data is not required under 35 U.S.C. §112. Throughout the present specification, there are substantial examples which teach the manner or process of making and using the invention in terms which enable skilled practitioners to practice the invention. Because the application discloses techniques that are readily available to those of ordinary skill in the art, it is respectfully submitted that one of ordinary skill in the art, being provided with sufficient guidance from Applicant's specification, would have an understanding of how to make and use the claimed invention. Accordingly, the lack of additional *in vivo* data does not support the conclusion that the application is not enabled.

At this early stage in the development of potentially useful compounds, it is not the function of the USPTO to decide what is clinically useful or to demand that Applicants demonstrate precise dosage regimes and clinical efficacy. One of ordinary skill in the art would be able to extrapolate from Applicants' mouse data to other mammals using no more than reasonable experimentation to modify the disclosed dosages and routes of administration.

Finally, the Office Action admits that an "understanding of the neurochemical substrates of learning and memory may require the analysis of actions on each of many individual processes...." The Examiner has failed to provide any evidence which shows the required "understanding" at the neurochemical level. Since the Examiner has failed to provide any analysis or evidence that casts any doubt on the objective truth of the statements contained in Applicants' disclosure and has admitted an inability to do so, the rejection lacks support and must be withdrawn.

Memory disorders, whether related to specific illnesses such as Alzheimer's Disease, or part of an overall cognitive decline associated with aging, are distinguishable by those skilled in the art by a subject's difficulty or inability in remembering or learning. Problems with spatial memory are frequently seen in such subjects, who forget where they are going or lose their way en route to a familiar destination. Anecdotal evidence of aged individuals becoming lost is plentiful.

Similar deficits in spatial memory can be demonstrated in mice and rats that are aged or have received organic brain damage correlated to that seen in Alzheimer's disease. The Morris Water Maze is a standard experiment used by those skilled in the art to test for problems with spatial memory and other deficiencies in cognition or learning ability (McNamara RL, Skeleton RW, *the Neuropharmacological and Neurochemical Basis of Place Learning in the Morris Water Maze*, Brain Res Brain Res Rev, 1993 Jan-Apr; 18(1):33-49).

Supporting the present application is mouse water maze test data which is correlated to the potential efficacy of compounds of the invention in the treatment of memory disorders associated with aging or specific conditions such as Alzheimer's disease. Aged mice exhibit deficiencies in spatial memory that can be observed and measured in the Morris Water Maze. The mice swim in convoluted indirect patterns as they search for the position of a submerged platform. Aged mice take much longer than younger mice, which remember the location and swim more directly toward the platform location and reach it much faster. Treatment with a compound of the invention significantly reduces the time it takes aged animals to find the platform, producing a clear improvement in the animals' spatial memory (Sauer H, Francis JM, Jiang H, Hamilton GS, Steiner JP., *Systemic Treatment with GPI 1046 Improves Spatial Memory and*

Reverses Cholinergic Neuron Atrophy in the Medial Septal Nucleus of Aged Mice, Brain Res, 1999 Sep 18; 842(1):109-18).

Treatments that show beneficial results in improving one component of memory disorder may not "cure" the disease outright or cause dramatic improvement in every aspect of impaired memory. However, even a compound that improves nothing more than spatial memory can be profoundly beneficial to a subject with a memory disorder. A person of ordinary skill in the art would understand that the Morris Water Maze test results are sufficient to show a correlation with memory disorders generally, in the absence of evidence to the contrary. Further, a person of ordinary skill in the art would understand that neither an examination of all stages or aspects of learning and memory, nor evidence of improvement in each, are necessary to prove this correlation.

The state of the art for the treatment of memory disorders includes several compounds known as cognitive enhancers. These compounds act on brain neurotransmitter receptors and are intended to restore normal receptor activity lost during aging or Alzheimer's disease, or to block abnormal activity that occurs in these states. An example of such a compound is Tacrine, an analog of the brain neurotransmitter acetylcholine. This compound has been shown to produce improvement in spatial memory deficits in rodents using the Morris Water Maze (Jackson JJ, Soliman MR,

Effects of Tacrine (THA) on Spatial Reference Memory and Cholinergic Enzymes in Specific Rat Brain Regions, Life Sci, 1996; 58(1):47-54). Tacrine is now used for treating age related cognitive deficits and Alzheimer's disease (Qizilbash N, Birks J, Lopez Arrieta J, Lewington S, Szeto S, *Tacrine for Alzheimer's Disease*, Cochrane Database Syst Rev, 2000; (3):CD000202 and Raskind MA, Sadowsky CH, Sigmund WR, Beitler PJ, Auster SB, *Effect of Tacrine on Language, Praxis, and Noncognitive Behavioral Problems in Alzheimer Disease*, Arch Neurol, 1997 Jul; 54(7):836-40).

That Applicants' compounds improve one or more of memory acquisition, retention, and/or retrieval is demonstrated. Which one of these stages is improved, and by what specific mechanism it is improved, are academic questions and do not address the legal issue at hand. Applicants' experimental data shows memory improvement in an appropriate animal model using an accepted protocol correlated to memory. The methods of treatment using the inventive compounds "improve memory" as claimed. Lacking a showing by the Examiner that improvement of specific stage(s) of learning and memory are required, an "understanding of the neurochemical substrates" and an identification of which stage(s) are in fact improved in the claimed methods are irrelevant.

As indicated in *In re Brana*, 34 U.S.P.Q.2D 1436, 1441 (Fed. Cir. 1995), it is inappropriate to reject claims based on *in vitro*

animal model example(s) based simply on a lack of *in vivo* data. In order to make such a rejection, the Examiner must introduce evidence that the animal model does not correlate with the claimed method. While the Examiner has provided evidence that the art of treating memory impairment is complicated, he has failed to provide any authority or evidence which proves that the Morris Water Maze test does not correlate with memory performance. Applicants' disclosure is sufficient to teach one of ordinary skill in the art how to make and use the invention.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

2. Rejection of Claim 1 under 35 U.S.C. §112, first paragraph

The Office Action rejects claim 1 under 35 U.S.C. §112, first paragraph, because the term "heterocyclic ester" renders the claim vague and indefinite.

Applicants respectfully traverse this rejection for the reason that 35 U.S.C. §112, first paragraph, relating to sufficiency of the disclosure to enable the invention, is not a proper basis for rejection of a claim for perceived indefiniteness.

Without waiving this deficiency, Applicants have amended claim 1, in order to describe the inventive subject matter more clearly and to advance prosecution of this application.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

CONCLUSION

Based upon the foregoing amendments and remarks, the presently claimed subject matter is definite, enabled, and patentably distinguishable over the art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of claims 1-4, 6, and 8-11, and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the pending claims is earnestly solicited.

The Examiner is invited to telephone the undersigned attorney if he has any questions or comments.

Respectfully submitted,

NATH & ASSOCIATES PLLC

Dated: November 16, 2000

By: _____
Gary M. Nath
Reg. No. 26,965
Todd L. Juneau
Reg. No. 40,669
Customer No. 20529

NATH & ASSOCIATES PLLC
1030 Fifteenth Street, NW
Sixth Floor
Washington, D.C. 20005
Telephone: (202) 775-8383
Facsimile: (202) 775-8396
GMN:TLJ:LCH RFR.wpd

ENDNOTES

---

[1] Immunophilin ligands have been proven to enhance the regeneration or regenerative sprouting of nerve fibers in both the peripheral and central nervous system (Steiner JP, Hamilton GS, Ross DT, Valentine HL, Guo H, Connolly MA, Liang S, Ramsey C, Li JH, Huang W, Howorth P, Soni R, Fuller M, Sauer H, Nowotnik AC, Suzdak PD. Neurotrophic immunophilin ligands stimulate structural and functional recovery in neurodegenerative animal models, Proc Natl Acad Sci USA, 1997 Mar 4; 94(5):2019-24). The eye has several distinct neural components. For example, the cornea is innervated by a plexus of thin c-fibers which transmit painful sensations when the cornea is irritated or scratched. Furthermore, the innervation of the pupil regulates the amount of light that enters the visual pathway. Innervation of the ciliary body allows the eye to accommodate and focus. The retina itself is an entirely neural structure that transduces light into neural impulses that exit the eye via the optic nerve en route to brain visual centers. The innervation of the extraocular muscles permits eye movement necessary for tracking and scanning visual stimuli. The innervation of the eyelids permits eye opening and closing. Injury or disease affecting any of the eyes' component tissues may result in either direct or secondary injury to the eyes neural components as one skilled in the art (an Ophthalmologist, who specializes in diseases of the eye) would recognize. The following table lists various types of nerve-related visual disorders, identifies for each general class of visual disorder a recognized disease or condition where neural components are affected, and cites at least one recent reference for each.

Vision disorder	Representative disease or condition	Reference for neural involvement in visual disorders caused by this disease
Orbital disorders	Retrobulbar hematoma	Gocer AI, Ildan F, Haciyakupoglu S, Tuna M, Bagdatoglu H, Polat S, Cetinalp E, Aksoy K. The effect of immediate decompression on the optic nerve in retrobulbar hematoma. Neurosurg Rev. 1996; 19(3):169-73.
	Fracture of the eye socket	Egbert JE, May K, Kersten RC, Kulwin DR. Pediatric orbital floor fracture: direct extraocular muscle involvement. Ophthalmology. 2000 Oct; 107(10):1875-9.
Disorders of the lacrimal apparatus	Sjogren's syndrome or "dry eye"	Waterman SA, Gordon TP, Rischmueller M. Inhibitory effects of muscarinic receptor autoantibodies on parasympathetic neurotransmission in Sjogren's syndrome. Arthritis Rheum. 2000 Jul; 43(7):1647-54.
Disorders of the eyelids	Facial nerve damage due to Hansen's disease (leprosy)	Kiran KU, Hogeweg M, Suneetha S. Treatment of recent facial nerve damage with lagophthalmos, using a semistandardized steroid regimen. Lepr Rev. 1991 Jun; 62(2):150-4.
	Blepharospasm	McCann JD, Gauthier M, Morschbacher R, Goldberg RA, Anderson RL, Fine PG, Digre KB A novel mechanism for benign essential blepharospasm. Ophthal Plast Reconstr Surg. 1999 Nov; 15(6):384-9.
Disorders of the conjunctiva	Haemorrhagic conjunctivitis	Wadia NH, Wadia PN, Katrak SM, Misra VP. A study of the neurological disorder associated with acute haemorrhagic conjunctivitis due to enterovirus 70. J Neurol Neurosurg Psychiatry. 1983 Jul; 46(7):599-610.
Disorders of the cornea	Epikeratophakia, cryokeratomileusis, keratomileusis in situ, photorefractive keratectomy, laser in situ keratomileusis, and phacoemulsification	Kohlhaas M Corneal sensation after cataract and refractive surgery. J Cataract Refract Surg. 1998 Oct; 24(10):1399-409. Review.
Cataract	Diabetes, cataract removal/lens implantation surgery	Bobrow JC. Cataract extraction and lens implantation with and without trabeculectomy: an intrapatient comparison. Trans Am Ophthalmol Soc. 1998; 96:521-56.
Disorders of the uveal tract	Uveitis	Merayo-Lloves J, Power WJ, Rodriguez A, Pedroza-Seres M, Foster CS. Secondary glaucoma in patients with uveitis. Ophthalmologica. 1999; 213(5):300-4.

Disorders of the retina	Macular degeneration	Roodhooft J. No efficacious treatment for age-related macular degeneration. Bull Soc Belge Ophtalmol. 2000; 276:83-92. Review.
	Glaucoma	Migdal C. Glaucoma medical treatment: philosophy, principles and practice. Eye. 2000 Jun; 14 (Pt 3b):515-8. Review.
Disorders of the optic nerve or visual pathways	Optic neuritis	Hood DC, Odel JG, Zhang X Tracking the recovery of local optic nerve function after optic neuritis: A multifocal VEP study. Invest Ophthalmol Vis Sci. 2000 Nov; 41(12):4032-8.
Free radical induced eye disorders and diseases	Age related macular degeneration	Beatty S, Koh H, Phil M, Henson D, Boulton M The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol. 2000 Sep-Oct; 45(2):115-34.
Immunologically mediated eye disorders	River blindness (onchocercal keratitis)	Hall LR, Pearlman E Pathogenesis of onchocercal keratitis (River blindness). Clin Microbiol Rev. 1999 Jul; 12(3):445-53. Review.
Eye injuries	Retinal damage due to child abuse	Kivlin JD, Simons KB, Lazoritz S, Ruttum MS. Shaken baby syndrome. Ophthalmology. 2000 Jul; 107(7):1246-54.
Visual impairments	General, arising from many ocular or neural conditions	Westall CA, Ainsworth JR, Buncic JR. Which ocular and neurologic conditions cause disparate results in visual acuity scores recorded with visually evoked potential and Teller Acuity Cards? JAAPOS. 2000 Oct; 4(5):295-301.
Symptoms and complications of eye disease, eye disorder or eye injury	Symptoms and complications of cataract surgery	Golnik KC, West CE, Kaye E, Corcoran KT, Cionni RJ. Incidence of ocular misalignment and diplopia after uneventful cataract surgery. J Cataract Refract Surg. 2000 Aug; 26(8):1205-9.
	Complications of glaucoma	Zhao DY, Cioffi GA. Anterior optic nerve microvascular changes in human glaucomatous optic neuropathy. Eye. 2000 Jun; 14 (Pt 3b):445-9.